REMARKS / ARGUMENTS

This Preliminary Amendment and Response to Final Office Action is filed concurrently with Applicant's RCE application of Serial No. 09/818,954, and is in response to the Final Office Action issued therein, dated July 11, 2003 (Paper No. 13).

Explanation of Amendments

Applicants respectfully request entry of the above amendments.

Claims 2, 3, and 50 have been amended. Claims 1-8, 10, 11, 47-51, 61, and 65 are currently pending. These amendments were not made in response to any prior art, and no new matter has been added by way of these amendments.

Rejection Under 35 U.S.C. § 101

Claims 1-8, 10, 11, 47-51, 61 and 65 remain rejected under 35 U.S.C. § 101. The Office Action asserts that the claimed invention is not supported by either a specific, substantial, and credible utility, or a well established utility.

The Official Action asserts that Applicants' transgenic data fails to establish utility. Applicants respectfully disagree.

Applicants' transgenic data demonstrate that mice overexpressing both the α2 and β10 subunits showed bilateral thyroid enlargement with multiple follicular papillary adenomas and a resultant hyperthyroidism, as indicated by elevated serum T4 levels. Thus, in a normal mouse setting, α2/β10 clearly has thyroid stimulating hormone (TSH) like activity. Due to the high level of amino acid conservation between mouse α2 and human α2 [88.5% identity and 90.4% similarity for the predicted mature forms (*i.e.*, without signal peptide)], the high level of amino acid conservation between mouse β10 and human β10 [93.4% identity and 97.2% similarity for the predicted mature forms (*i.e.*, without the signal peptide)], and the very high level of similarity between mouse thyroid gland biology and human thyroid gland biology, human α2/β10 heterodimer would be predicted to have the same thyroid stimulating hormone (TSH) like activity as that found for the mouse α2/β10 heterodimer.

TSH, for example, influences basal metabolism by regulating the production of thyroid hormones and is used clinically for enhancing the detection and treatment of thyroid carcinoma;

see McEvoy, G. (ed.), *AHFS Drug Information*, pp. 2041-2042, American Soc. of Health-System Pharmacists, Inc., Bethesda, MD (1998). In addition, diagnostic tests for measuring TSH levels in the blood are commonly used in the art for determining the functional status of the thyroid gland when thyroid gland disorder is suspected. Human α2/β10 would thus have similar clinical (and other) utilities as TSH, and is therefore useful for, *e.g.*, the treatment and diagnosis of thyroid gland-related diseases and disorders, as well as the additional therapeutic and diagnostic uses as described in the application. For example, human α2/β10 selective binding agents (such as antibodies), would have similar utility to selective binding agents with specificity to TSH, and are therefore useful for the treatment and diagnosis of thyroid gland related diseases and disorders.

Confirming the utility of Applicants' discovery, that the α2/β10 heterodimer has thyroid stimulating hormone (TSH) like activity, are the recent results reported in 2002 by a research group at Stanford University [Nakabayashi *et al.*, Thyrostimulin, a heterodimer of two new human glycoprotein hormone subunits, activates the thyroid-stimulating hormone receptor, *J. Clin. Invest.* 109:1445-1452 (2002)]. Nakabayashi *et al.* was cited In Applicants' Supplemental IDS dated October 15, 2002, and while subsequent to Applicants filing, describes the same heterodimer described in Applicants' disclosure. Applicants note that Nakabayashi's α2 (termed "A2"; see their Figure 1a) is the same as Applicants' α2, and Nakabayashi's β5 (also their Figure 1a) is the same as Applicants' β10. A BestFit comparison is set forth as Appendix A to this Amendment.

Nakabayashi *et al.* state:

> Based on its thyroid-stimulating property, this purified heterodimeric protein was named thyrostimulin to distinguish it from the known thyroid-stimulating hormone, TSH.

and:

> Based on the dimerization of two new glycoprotein hormone subunits, we have identified a novel heterodimeric glycoprotein hormone capable of activating TSH receptors in vitro and in vivo.

Consistent with the utility described in Applicants' disclosure, Nakabayashi *et al.* state the following:

> Recombinant human TSH has been used to facilitate the monitoring for thyroid carcinoma. Because the A2/B5 heterodimer showed potent TSH-like bioactivity in vivo, the availability of recombinant thyrostimulin provides an additional diagnostic tool for thyroid tumors.

Additionally, as noted in Applicant's previous response, in individuals producing an undesired excess of α2, and/or β10 and/or the α2/β10 heterodimer, the utility is specific (thyroid enlargement, multiple follicular papillary adenoma, hyperthyroidism), substantial (these are not insignificant conditions), and credible (one skilled in the art would not have any reason to question the utility in view of the level of skill in the art combined with Applicants' teachings). The Examiner asserts that the transgenic data is somehow not persuasive, and adds that the "ability to cause thyroid enlargement, multiple follicular papillary adenoma and hyperthyroidism" does not demonstrate utility, but "merely is a tantalizing finding that invites further experimentation."

Applicants invention does not relate *per se* to an ability to cause thyroid enlargement, multiple follicular papillary adenoma and hyperthyroidism. Instead, Applicants transgenic data represent evidence recognized by those skilled in the art that the molecules discovered by Applicants have utility. It must be emphasized that one skilled in the art would find such transgenic data crucial in the identification of the therapeutic uses for these molecules.

Where a patient demonstrates undesired levels of α2, and/or β10, and/or the α2/β10 heterodimer, and displays the accompanying symptoms of, for example, thyroid enlargement, multiple follicular papillary adenoma, and/or hyperthyroidism, one skilled in the art would know to administer an antagonist (*e.g.*, a selective binding agent) to α2, and/or β10, and/or the α2/β10 heterodimer to treat these conditions. Similarly, where a patient displays lower-than-desired levels of α2, and/or β10, and/or the α2/β10 heterodimer, one skilled in the art would recognize that it would be efficacious to administer one or both of these molecules (for example as the heterodimer) to the patient to achieve the desired therapeutic effect.

Applicants wish to point out that the standards for utility in a patent application are quite different than those set forth by a regulatory agency, such as the FDA. Until a molecule reaches human clinical trials, transgenic mouse experiments such as those contained in Applicants' patent application, are art-recognized as one standard method to identify the use (utility), of a molecule.

Reconsideration of this rejection is respectfully requested.

Rejections Under 35 U.S.C. § 112

Claims 1-8, 10, 11, 47-51, 61 and 65 also are rejected under 35 U.S.C. § 112, first paragraph. The Office Action asserts that if the claimed invention is not supported by either a specific, substantial and credible asserted utility, or a well established utility, one skilled in the art would not know how to use the claimed invention. Because Applicants have demonstrated above that the invention does in fact have adequate utility, and withdrawal of the rejection under 35 U.S.C. § 112 is requested.

Claims 1-8, 10, 11, 47-51, 61 and 65 are also rejected under 35 U.S.C. § 112 first paragraph as containing subject matter which assertedly was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Office Action states that there is insufficient written description to support "β10" from any species, as well as variants thereof. The Office Action adds that the specification assertedly does not specify what "β10 activity" is. The Office Action also states that Applicants did not point out where the percent similarity of human and mouse β10 can be found in the specification.

Applicants' specification describes β10 molecules from both human and non-human species, and what the activity is thereof. In addition to Figure 4 (cited by Applicants in their previous response) support can also be found on, *e.g.*, page 10, lines 2-17, the specification which sets forth the percent identity/similarity between mouse and human β10 as follows, and further describes the relevant activity:

> Due to the high level of amino acid conservation between mouse α2 and human α2 [88.5% identity and 90.4% similarity for the predicted mature forms (i.e. without signal peptide)], the high level of amino acid conservation between mouse β10 and human β10 [93.4% identity and 97.2% similarity for the predicted mature forms (i.e. without signal peptide)], and the very high level of similarity between mouse thyroid gland biology and human thyroid gland biology, it is anticipated that human α2/β10 heterodimer has the same thyroid stimulating hormone (TSH) like activity as that found for the mouse α2/β10 heterodimer. (*Emphasis added*).

This TSH-like activity, and other significant activities, are fully described throughout Applicants' specification. These include, but are not limited to, thyroid gland related diseases and disorders (e.g., bilateral thyroid enlargement, follicular papillary adenomas, hyperthyroidism, etc.).

Additionally, Applicants direct the Examiner's attention to page 5, lines 32-33, and page 6, lines 1-15:

> Further, GAP analysis indicated that the homology of β10 to the four known human glycoprotein hormone β-subunits (mentioned above) was 31-37% identity and 42-48% similarity (see Figure 2A-D, referred to hereinbelow). The mature forms of the four known human β-glycoprotein hormone polypeptides contain twelve cysteine residues, which form six intramolecular disulfide bonds. The mature form of the human β10 polypeptide of the present invention contains ten cysteine residues, which are likely to form five intramolecular disulfide bonds. Using the disulfide bond cysteine pairing of CG- β as a model, the most likely disulfide bond cysteine pairing for the five putative disulfide bonds in the β10 polypeptide of this invention is as follows: C12-C60, C26-C75, C36-C91, C40-C93 and C96-C103 of SEQ ID NO: 3 (see also Figure 3).

Given the β10 activity as described in Applicants' specification, and the high (93.4%) identity between murine and human β10, as well as the homology comparison of β10 to the four known human glycoprotein hormone β-subunits in both the description and in Figures 2A-D and Figure 3, one skilled in the art can readily predict variants, etc. which retain the claimed β10 activity. To require Applicants to restrict their claims to a specific number of changes would be to unnecessarily limit the scope of the invention, and to invite infringement by third parties. Withdrawal of this rejection is respectfully requested.

Claim 50 is rejected under 35 U.S.C. § 112, first paragraph as containing subject matter allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is said to be a new matter rejection.

Claim 50 as amended now reads as follows:

> 50. A fusion polypeptide comprising a polypeptide encoded by a nucleic acid molecule of Claims 1, 2, or 3 fused to a heterologous amino acid sequence.

The Examiner feels that there is no basis in the specification as originally filed for concatameric fusion proteins. Applicants disagree, and maintain that one skilled in the art can readily make concatameric fusion proteins with Applicants' teaching in hand. Nevertheless, in the interest of expediting prosecution, Applicants have amended Claim 50 to more specifically point out the invention described by Claim 50, that is, a fusion polypeptide comprising a polypeptide encoded by a nucleic acid molecule as described in Claims 1, 2, or 3, and fused to a heterologous amino acid sequence.

Claims 1-8, 10, 11, 47-51, 61, and 65 remain rejected under 35 U.S.C. § 112 second paragraph, as assertedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Those claims that recited "moderately" or "highly" stringent conditions are said to be indefinite. The Office Action asserts that there lacks a limiting definition of these conditions in the specification.

The term "highly stringent conditions" is fully described at page 31, lines 20-33:

> The term "highly stringent conditions" refers to those conditions that are designed to permit hybridization of DNA strands whose sequences are highly complementary, and to exclude hybridization of significantly mismatched DNA's. Hybridization stringency is principally determined by temperature, ionic strength, and the concentration of denaturing agents such as formamide. Examples of "highly stringent conditions" for hybridization and washing are 0.015M sodium chloride, 0.0015M sodium citrate at 65-68°C or 0.015M sodium chloride, 0.0015M sodium citrate, and 50% formamide at 42°C. See Sambrook, Fritsch & Maniatis, Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory, (Cold Spring Harbor, N.Y. 1989); Anderson *et al.*, Nucleic Acid Hybridisation: a practical approach, Ch. 4, IRL Press Limited (Oxford, England).

Moderately stringent conditions are thoroughly described at page 33, lines 12-21:

> The term "moderately stringent conditions" refers to conditions under which a DNA duplex with a greater degree of base pair mismatching than could occur under "highly stringent conditions" is able to form. Examples of typical "moderately stringent conditions" are 0.015M sodium chloride, 0.0015M sodium citrate at 50-65°C or 0.015M sodium chloride, 0.0015M sodium citrate, and 20% formamide at 37-50°C. By way of example, a "moderately stringent" condition of 50°C in 0.015M sodium ion will allow about a 21% mismatch.

These definitions are art-recognized, and are fully described and defined in accordance with the state of the art in the year 2000. One skilled in the art can readily determine the metes

and bounds of the terms "moderately stringent conditions" and "highly stringent conditions" based on the definitions in Applicants' specification. While reference to textbooks and recitation of exemplary conditions is apparently objected to by the Office Action, Applicants are aware of no prohibition against the use of textbooks and detailed examples to further define a term in a patent specification. These provide further guidance to one skilled in the art, for otherwise routine hybridization techniques, and should not be used as the basis of a rejection by the USPTO. Withdrawal of this rejection is thus requested.

Claim 2 is said to remain indefinite with respect to part (d). The nature of the 'fragment of at least 16 nucleotides' is said to be unclear. In response thereto, Applicants have amended part (d) of Claim 2 to recite:

> (d) a nucleotide sequence of SEQ ID NO: 2 or (a)-(c) comprising a fragment of at least about 16 nucleotides thereof;

This rejection is said to further apply to other claims, for example claim 3, part (f). Applicants have amended claim 3 in a similar manner. These amendments were not made in response to any prior art, and withdrawal is respectfully requested.

Claim 3 is said to remain indefinite for failing to adequately point out that which applicant sees as the invention. The Office Action states that there is no upper limit given to the number of substitutions, insertions, deletions, or truncations recited therein.

Applicants note that Claim 3 specifically requires that the recited polypeptides, whether they be substitution, insertion, deletion, or truncation variants, when heterodimerized to human α2 polypeptide have an activity of the human α2/β10 heterodimer. As noted above, Applicants' specification describes the high (93.4%) identity between murine and human β10, as well as a homology comparison of β10 to the four known human glycoprotein hormone β-subunits (see also Figures 2A-D and Figure 3). With this knowledge in hand, coupled with the additional teachings in Applicants specification, one skilled in the art can readily predict substitution, insertion, deletion, or truncation variants which retain the claimed β10 activity. To require Applicants to restrict their claims to a limited number of specific changes would be to unnecessarily limit the scope of the invention, and invite infringement by third parties. Withdrawal of this rejection is respectfully requested.

Claim 8 is said to remain indefinite for assertedly failing to adequately point out that which Applicants see as their invention. Claim 8 recites a "β10 polypeptide" that is to be

produced, whereas the claims from which it depends are said not to provide antecedent basis for the recitation of "β10" polypeptide.

In response thereto, for purposes of clarity, Applicants have removed the term "β10" from the preamble (the only instance where the term "β10 polypeptide" occurs). The amendment was not made in response to any prior art, and simply makes the claim more consistent with the previously used terms in claims from which Claim 8 depends.

Claim 61 is said to remain indefinite. The metes and bounds of "human β10 polypeptide" are said to be unclear; the Office Action asserts that the specification does not breathe life and meaning into the term. In response thereto, Applicants direct the Examiner's attention to the following sections of the specification:

- Page 18, lines 29-31, and page 19, lines 1-2: "FIGURE 1 depicts in linear array the full coding region of human ß10 polypeptide in accordance with this invention (SEQ ID NO: 1). The predicted signal peptide region is underlined and the region containing the predicted signal peptide cleavage site is boxed."

- Page 6, lines 3-9: "The mature forms of the four known human ß glycoprotein hormone polypeptides contain twelve cysteine residues, which form six intramolecular disulfide bonds. The mature form of the human ß10 polypeptide of the present invention contains ten cysteine residues, which are likely to form five intramolecular disulfide bonds."

- Page 6, lines 24-28: "BestFit analysis indicated that the amino acid homology of mature form human ß10 polypeptide as compared to mature form mouse ß10 polypeptide was 93.4% identity and 97.2% similarity (see Figure 4, referred to herein below)."

- Page 7, lines 10-15: "A heterodimerization assay was used to determine that human ß10 forms a heterodimer with human α2 polypeptide, described in the above mentioned WO99/41377 and WO 00/78964 patent applications, thus discovering and defining a novel heterodimeric glycoprotein hormone, α2/ß10."

The Figures also show sequence overlap with other known family members. For example, Figure 2A shows an overlap of human TSH-β and human β10, with percent identity and identification of their common amino acids. Figure 2B shows an overlap of human FSH-β and human β10, and Figure 2C shows an overlap of human LH-β and human β10, with percent identity and identification of their common amino acids. Figure 2D shows an overlap

of human CG-β and human β10 with percent identity and identification of their common amino acids.

Applicants respectfully submit that the metes and bounds of the term, "human β10 polypeptide" are not unclear and can be readily determined by one skilled in the art in view of Applicants' disclosure. Withdrawal is respectfully requested.

Rejection Under 35 U.S.C. § 102(b)

Claims 1-5, 7, and 11 are rejected under 35 U.S.C.§ 102(b) as being allegedly anticipated by Mahairas *et al.*, Locus AQ495547 (4/18/99).

As noted in Applicants' previous response, in order to invalidate a claim for anticipation under 35 U.S.C. § 102, a single cited reference must identify each and every feature recited in the claim sought to be invalidated. *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991); *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Additionally, in order for a reference to be effective under 35 U.S.C. § 102, the reference must contain an enabling disclosure. See *In re Hoeksma*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968); MPEP § 2121.1.

Moreover, the identical invention must be shown in as complete detail as is contained in the Applicant's claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1920 (Fed. Cir. 1989), and a claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003). To be anticipatory, the reference must also enable one of skill in the art to both make and use the claimed invention. *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566, 37 USPQ2d 1618, 1624 (Fed. Cir. 1996).

As noted previously, Mahairas describes a BAC clone containing a piece of human genomic DNA. The sequence in Mahairas is completely unannotated, and importantly, identifies no reading frame, no cloning orientation (5' or 3'), no introns, exons, genes, or homologies to other molecules. Additionally, cysteines C12, C36, and C40 are critical the activity of the molecule, are encoded by exon 1, and are not present in the portion of the truncated β10 polypeptide encoded by the Mahairas sequence.

Thus, not only does the Mahairas reference lack any description of the mature form of β10 polypeptide, but it would not be able to adopt a cystine-knot configuration. The 3-dimensional structure of the significantly truncated Mahairas polypeptide would be completely unlike that of mature β10 polypeptide and the Mahairas polypeptide would be completely inactive with regards to heterodimerizing with α2 polypeptide and binding to the α2/β10 receptor(s).

The previous Office Action admits that it cannot be determined whether the molecule from Mahairas possesses the properties recited in the claims, and further acknowledges that it cannot be determined whether it is sufficient to heterodimerize with α2. The present Office Action states, however, that the claims recite an "activity" of the human α2/β10 heterodimer, and that antibody binding is an "activity." The Office Action then speculates, with no supporting evidence, that the sequence disclosed in Mahairas would comprise an antibody binding epitope.

It must be noted that the Patent and Trademark Office bears the burden of supporting its rejections, and the nature of such rejections must be stated with particularity. *See* MPEP §707.07(D). The Office Action has provided no support for the assertion that the sequence described in Mahairas would contain any epitopes whatsoever. Applicants acknowledge that the Examiner is required to give claims their broadest reasonable interpretation when applying art, however (and as noted above) the 3-D structure of the significantly truncated Mahairas β10 polypeptide would be completely unlike that of the mature β10 polypeptide. Absent evidence from the Patent and Trademark Office to the contrary, there is simply no basis for the arbitrary conclusion that Mahairas contains any epitopes, let alone would possesses any "activity" as claimed by Applicants.

Withdrawal of this rejection is requested.

Rejection Under 35 U.S.C. § 103(a)

Claims 6, 8, and 48-50 remain rejected under 35 U.S.C. § 103(a) as being allegedly obvious over Mahairas, above, in view of Sibson *et al.*, WO 94/01548.

Sibson *et al.* is said to teach the use of a desired cDNA sequence into an expression vector, host cell, and express the encoded protein, as well as to raise antibodies to proteins encoded by such DNAs.

Claim 6 relates to a eukaryotic host cell comprising a vector, wherein the vector comprises the nucleic acid molecules set forth in Claims 1, 2, or 3. Claim 8 describes a process of producing a β10 polypeptide comprising culturing a host cell of under suitable conditions to express the polypeptide, and then optionally isolating the polypeptide from the culture. Claims 48-50 relate to viral vectors containing Applicants' nucleic acid molecules, and fusion polypeptides comprising a polypeptide encoded by the nucleic acid molecules fused to a heterologous amino acid sequence.

The Office Action asserts on page 8, lines 25-27, that Sibson is directed to "DNAs such as that disclosed by Mahairas, which are obtained by cDNA cloning..." Mahairas was addressed in detail previously and above, but Applicants reiterate that Mahairas describes a random piece of genomic DNA, not a cDNA. Mahairas' genomic DNA was not obtained by cDNA cloning.

As discussed in applicants previous response, elements of separate patents (or publications) cannot be combined when there is no suggestion of such combination anywhere in those patents (or publications)... and a court (or the PTO) should avoid hindsight). *Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1 USPQ2d 1593, (Fed. Cir. 1987), citing *ACS Hospital Systems,* 220 USPQ 929, 933 (Fed Cir 1984). Additionally, either the references must expressly or impliedly suggest the claimed invention, or the examiner must present a convincing line of reasoning as to why one skilled in the art would have found the claimed invention to be obvious in light of the teachings of the references. *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Intf. 1985); *See also* MPEP 2144-2144.09.

An analysis under 35 U.S.C. § 103 requires consideration of (*i*) whether the prior art would have suggested to one skilled in the art that they should make the claimed composition, and (*ii*) whether the prior art would have revealed a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991), *citing In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). However, both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's own disclosure. *Id.*

Mahairas describes incomplete, genomic DNA, with an intron (and absolutely no reading frame or orientation) corresponding to an *inactive* portion of the β10 molecule, which simply would not fold properly. Sibson relates to completely *unrelated* cDNA sequences (*i.e.*, not genomic DNA), and methods of producing the same. There is simply no suggestion whatsoever

in the cited references of such a combination with genomic DNA fragments, let alone a β10 genomic DNA fragment.

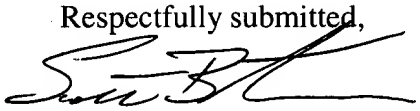
There is absolutely no suggestion in the cited references to combine Mahairas and Sibson. Even if one skilled in the art were motivated to combine these references (and Applicants maintain they would not) the combination of Mahairas and Sibson would have at best resulted in a misfolded, inactive peptide fragment. What one would *not* have, however, would be Applicants' invention as claimed in Claims 6, 8, and 48-50.

Withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the amendment and remarks made herein, Applicants believe that pending claims 1-8, 10, 11, 47-51, 61, and 65 are now in condition for allowance, and respectfully request reconsideration.

Respectfully submitted,



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APPENDIX A

1. BEST FIT COMPARISON OF AMGEN α2 AND NAKABAYASHI α2 (FIG1A *JCI* 2002)

BLOSUM62 amino acid substitution matrix.
Reference: Henikoff, S. and Henikoff, J. G. (1992). Amino acid substitution matrices from protein blocks. Proc. Natl. Acad. Sci. USA 89: 10915-10919.

Gap Weight:	8	Average Match:	2.778
Length Weight:	2	Average Mismatch:	-2.248
Quality:	687	Length:	129
Ratio:	5.326	Gaps:	0
Percent Similarity:	100.000	**Percent Identity:**	**100.000**

Match display thresholds for the alignment(s):
| = IDENTITY
: = 2
. = 1

Amgen α2 vs. Nakabayashi α2 (Fig1a JCI 2002)

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          .         .         .         .         .
  1 MPMASPQTLVLYLLVLAVTEAWGQEAVIPGCHLHPFNVTVRSDRQGTCQG 50
    ||||||||||||||||||||||||||||||||||||||||||||||||||
  1 MPMASPQTLVLYLLVLAVTEAWGQEAVIPGCHLHPFNVTVRSDRQGTCQG 50
          .         .         .         .         .
 51 SHVAQACVGHCESSAFPSRYSVLVASGYRHNITSVSQCCTISGLKKVKVQ 100
    ||||||||||||||||||||||||||||||||||||||||||||||||||
 51 SHVAQACVGHCESSAFPSRYSVLVASGYRHNITSVSQCCTISGLKKVKVQ 100
          .         .
101 LQCVGSRREELEIFTARACQCDMCRLSRY 129
    |||||||||||||||||||||||||||||
101 LQCVGSRREELEIFTARACQCDMCRLSRY 129
```

2. BEST FIT Comparison of Amgen β10 vs. Nakabayashi β5 (Fig1a JCI 2002)

BLOSUM62 amino acid substitution matrix.
Reference: Henikoff, S. and Henikoff, J. G. (1992). Amino acid substitution matrices from protein blocks. Proc. Natl. Acad. Sci. USA 89: 10915-10919.

Gap Weight:	8	Average Match:	2.778
Length Weight:	2	Average Mismatch:	-2.248
Quality:	722	Length:	130
Ratio:	5.554	Gaps:	0
Percent Similarity:	100.000	**Percent Identity:**	**100.000**

Match display thresholds for the alignment(s):
| = IDENTITY
: = 2
. = 1

Amgen β10 vs. Nakabayashi β5 (Fig1a JCI 2002)

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                .         .         .         .         .
      1 MKLAFLFLGPMALLLLAGYGCVLGASSGNLRTFVGCAVREFTFLAKKPGC 50
        |||||||||||||||||||||||||||||||||||||||||||||||||||
      1 MKLAFLFLGPMALLLLAGYGCVLGASSGNLRTFVGCAVREFTFLAKKPGC 50
                .         .         .         .         .
     51 RGLRITTDACWGRCETWEKPILEPPYIEAHHRVCTYNETKQVTVKLPNCA 100
        ||||||||||||||||||||||||||||||||||||||||||||||||||||
     51 RGLRITTDACWGRCETWEKPILEPPYIEAHHRVCTYNETKQVTVKLPNCA 100
                .         .         .
    101 PGVDPFYTYPVAIRCDCGACSTATTECETI 130
        |||||||||||||||||||||||||||||||
    101 PGVDPFYTYPVAIRCDCGACSTATTECETI 130
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